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Digital Anomalies, Microcephaly, and Normal Intelligence: New Syndrome or Feingold Syndrome?

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We present four patients—two boys and their mother and an unrelated girl—with microcephaly, normal intelligence, and digital abnormalities. The hand abnormalities are characterized by brachydactyly with radial clinodactyly of the fourth and fifth fingers, ulnar clinodactyly of the second fingers, and an increased space between the second and third fingers associated with an abnormal palmar crease that extends to the ulnar border. The foot abnormalities include short toes with syndactyly of the fourth and fifth toes. The mother has normal intelligence, and her sons and the unrelated girl have normal development. Although similar digital abnormalities, microcephaly, and normal intelligence were described by Feingold in patients with gastrointestinal atresia, we think that our patients' findings represent a different condition. The most likely mode of inheritance is autosomal dominant. The clinical recognition of this syndrome will allow for appropriate genetic counseling as well as provision of information on natural history, i.e., normal intelligence. Am. J. Med. Genet. 69:240-244, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: microcephaly; digital abnormalities; brachydactyly; syndactyly

INTRODUCTION

Microcephaly, which can be seen in isolation or in association with multiple congenital anomalies, is frequently associated with mental retardation [Opitz and Holt, 1990]. We report on two boys and their mother, and an unrelated girl with microcephaly, normal intelligence, and symmetrical digital abnormalities. We think that their findings represent a distinct clinical syndrome that is autosomal dominant in inheritance. Recognition of this condition allows for appropriate genetic counseling and information on natural history, i.e., normal intelligence.

CLINICAL REPORT

Patient 1

The propositus is an 18-month-old boy seen initially for short stature and hand and foot anomalies. He was born at 36 weeks of gestation by induced vaginal delivery. Pregnancy was complicated by poor weight gain. Intrauterine growth retardation was detected within the last month of gestation, so labor was induced. At delivery, a nuchal cord was detected as well as a small placenta. Birth weight was 2.1 kg (10th–25th centile), and length 43.2 cm (10th centile). His birth OFC was not available. Hand and foot anomalies were noted, but no other malformations were observed.

Developmentally, he rolled over at 7 months, sat without support at 9 months, and walked at 14 months. At 18 months, he walked well and used 5–10 words appropriately. His growth velocity was normal.

On examination, his length was 76 cm (<5th centile for age, 50th centile for a 12 month), weight 8.9 kg (<5th centile, 50th centile for 8 1/2 months), and OFC 42.5 cm (<2nd centile, 50th centile for 4 1/2 months). He was proportionate. His cranial configuration was normal and symmetrical. His eyes appeared slightly large but were placed normally (Fig. 1). No abnormalities of the chest or abdomen were noted. He had full range of motion of the large joints. His hands and feet were symmetrically involved. There was the appearance of brachydactyly of the second, fourth, and fifth fingers with radial clinodactyly of the fourth and fifth fingers, and ulnar clinodactyly of the second fingers. The third fingers were long. Hand length was 9.3 cm (3rd–25th centile), middle finger length was 4.8 cm (97th centile), and ratio of middle finger to total hand was 0.52 (>97th centile). There was a single flexion crease of the fifth finger and an increased space between the second and third fingers with an associated crease that extended to the ulnar border (Fig. 2). He had short toes with syndactyly of the fourth and fifth toes and mild syndactyly of the second and third toes (Fig. 3). He had one hypopigmented macule on his

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Fig. 1. Patients 1, 2, and 3. Note microcephaly.

wrist. External genitalia were normal. His neurological status was unremarkable.

Radiographs of the hands showed small middle phalanges of the second, fourth, and fifth fingers, and clinodactyly of the second, fourth, and fifth fingers. Foot radiographs showed absence of the middle phalanges of all toes. Skull radiographs indicated no evidence of craniosynostosis. Chromosomes of peripheral blood were normal (46,XY) in 21 metaphases examined at the 550–600 band level using G banding.

Patient 2

Patient 2 is the 20-year-old mother of patient 1. She had normal intelligence and no significant past medical history. Her height was 165.1 cm (50–75th centile), and OFC 49 cm (significantly below second centile for adult female). Her hand and foot abnormalities were similar to her son's and were symmetrical. Her hand length was 17.6 cm (25–50th centile), middle finger length was 8 cm (75–97th centile), and ratio of middle finger to total hand was 0.45 (75–97th centile). She had short fifth fingers. The middle fingers appeared to be long. The other fingers appeared to be normal. She also had

Fig. 2. Hands of patient 1 (right) and 2 (left). Digital abnormalities are described in text.

Fig. 3. Feet of patient 1 (right) and 2 (left). Note significant shortening and syndactyly 4–5 toes.

an increased space between the second and the third fingers with an abnormal palmer crease (Fig. 2). She had significant shortness and syndactyly of the fourth and fifth toes. She had also mild syndactyly of the second and third toes (Fig. 3).

Family history was unremarkable with no other relatives with microcephaly or digital abnormalities.

Patient 3

Patient 3 was born after evaluation of patients 1 and 2. He was evaluated at 8 months of age and was noted to have findings similar to his brother and mother (Fig. 1). OFC was 39.5 cm (<5th centile, 50th centile for 3 months). There was the appearance of clinobrachydactyly of the fourth and fifth fingers and an increased space between the second and third fingers with an associated crease. Syndactyly between the fourth and fifth toes was noted bilaterally.

Patient 4

This 18-month-old girl was referred for microcephaly and digital abnormalities. She was born to a 35-year-old healthy mother at 40 weeks of gestation. Oligohydramnios diagnosed at 18 weeks of gestation by ultrasound examination resolved after 6 weeks of bedrest. Her birth weight was 3490 g (75–90th centile), length 50 cm (75th centile) and OFC 33.5 cm (50th centile). There were no neonatal problems. At age of 8 months, she was noted to have microcephaly but normal neurological findings. At that time, skull films and eye findings were normal. Family history was unremarkable.

On examination, her length was 80 cm (25–50th centile), weight 10.5 kg (25–50th centile), and OFC 44 cm (below the 5th centile, 50th centile for 8 months). Cranial configuration was small but symmetrical. She had epicanthal folds, but her face was otherwise normal (Fig. 4). Her chest and abdomen were normal. Her large joints were normal with full range of motion. She had bilateral clinodactyly of the second, fourth, and fifth fingers with a single flexion crease of the fifth

Fig. 4. Patient 4. Note microcephaly.

Fig. 6. Foot of patient 4. Note shortening and syndactyly 4–5 toes.

fingers (Fig. 5). She had marked shortness and syndactyly of fourth and fifth toes bilaterally (Fig. 6). Her skin was unremarkable. Her neurological status was normal.

Developmentally, she sat at 8 months, crawled at 8 months, and walked at 12 months. At 18 months of age, she used "mama" and "dada" specifically. She understood simple commands and had no unusual behaviors.

DISCUSSION

One of the distinctive anomalies of our patients, which is important for specific clinical diagnosis, is their digital defects characterized by brachydactyly and clinodactyly of the second, fourth, and fifth fingers and syndactyly of the fourth and fifth toes. The hand anomalies of our patients can be broadly classified as type A brachydactyly, which is characterized by shortness of the middle phalanges (brachymesophalangy) [Bell, 1951; Winter et al., 1993]. Subtypes of brachydactyly type A have been identified. Type A1 is characterized by shortness of all the middle phalanges of the fingers and toes, radial clinodactyly of fourth and fifth fingers, and ulnar clinodactyly of second and third fingers. The degree of shortness is variable. The feet show a similar pattern of abnormalities with absent or rudimentary middle phalanges. Type A4 is thought to be a mild type of type A1, consisting of shortness of middle phalanges of the second and fifth fingers [Fitch, 1979]. The clinical and radiographic findings of patient 1 are consistent with the findings in brachydactyly type A1 or A4 (Fig. 7), but in patient 2 (his mother) and patient 4, brachydactyly is limited to the fifth fingers, characteristic of type A3. Interestingly, the abnormal palmar crease in patients 1, 2, and 3 are identical to those in the patients with brachydactyly type A1 [Temtamy and McKusick, 1978]. Syndactyly of the fourth and fifth toes is not an associated findings in brachydactyly type A1, A3, or A4 [Bell, 1951; Temtamy and McKusick, 1978; Fitch, 1979].

Fig. 5. Hand of patient 4. Note shortening of the fifth finger and clinodactyly of 2,4,5 digits.

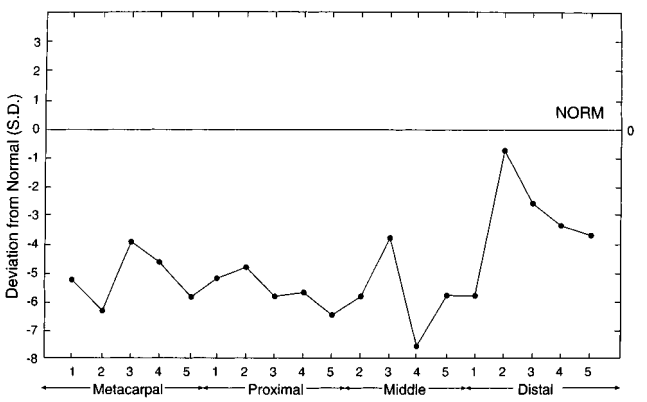

Fig. 7. Metacarpophalangeal profile analysis: Patient 1.

Microcephaly can be seen in isolation or in association with other congenital anomalies (syndromic). Mental retardation is frequently associated. In some microcephaly syndromes, various forms of digital anomalies are described. Feingold [1975, 1978] reported two families with microcephaly, normal intelligence, and digital abnormalities. In the first family, all affected members had microcephaly, clinodactyly of the fifth fingers, and syndactyly of the second and third toes. The propositus of this family also had tracheoesophageal fistula and minor anomalies (short palpebral fissures, micrognathia, and apparently low-set ears). The second family had similar digital abnormalities and microcephaly with normal intelligence, but none was described to have intestinal atresia. Subsequently, Konig et al. [1990] and Brunner and Winter [1991] reported families that may have the same syndrome. In their families, the consistent digital abnormalities were clinodactyly of the fifth fingers and syndactyly of the fourth and fifth toes. Syndactyly of the second and third toes was also described but appeared less prominent. In those families, 7 of 16 members had either esophageal or duodenal atresia. Intelligence in those patients appeared normal, although some individuals in the first family reported by Brunner and Winter [1991] needed "special school." It should be mentioned that microcephaly did not segregate with the digital abnormalities in this particular family. We think our patients have a different condition from those described with intestinal atresia, which we propose to call Feingold syndrome. The second family described by Feingold [1978] appears to be more similar to our patients than those patients with intestinal atresia. Conversely, whereas our patients do not have minor facial anomalies and intestinal atresia, their digital abnormalities are quite similar, and we cannot exclude the possibility that this represents variant of the same condition. The clinical findings of our patients and those previously reported are summarized in Table I.

Kelly et al. [1993] reported on two brothers with microcephaly and severe mental retardation and symmetric digital anomalies. Their digital anomalies included brachydactyly of the fifth fingers and syndactyly of the fourth and fifth toes. Their patients had specific facial anomalies and bilateral hallux valgus. Severe mental retardation was not seen in our patients, which would suggest that they do not have this condition. Syndactyly and microcephaly are also components of Filippi syndrome, which includes growth retardation, characteristic facial appearance, microcephaly, mental retardation, syndactyly of the second and third fingers, and significant syndactyly of the second, third, fourth, and fifth toes [Filippi, 1985; Meinecke, 1993; Toriello and Higgins, 1995]. However, our patients do not have severe syndactyly of the second and third fingers and toes, severe growth retardation, or minor facial anomalies (Table II).

Microcephaly and similar digital abnormalities can be seen in patients with various deletions and some craniosynostosis syndromes. These conditions easily can be eliminated from the differential diagnosis by the presence of normal chromosomal analysis and lack of other cardinal anomalies.

The transmission of these findings from mother to two sons is most suggestive of autosomal dominant inheritance. Although X-linked inheritance is possible, we think that this is unlikely given similar degree of involvement in the mother and both of her sons and the unrelated girl.

From the point of view of genetic counseling, identification of this specific clinical syndrome will allow for useful prognostic information to patients, particularly such as the sporadically occurring case, patient 4, in which there is presumably a new gene mutation. We expect patients to have normal intelligence, and we would predict that patient 4's parents have a low recurrence risk, but that her recurrence risk is 50%.

TABLE I. Clinical Manifestations in Our Patients and in Patients With Feingold Syndrome

	Our patients				Feingold syndrome				
					Feingold [1975, 1978]		Konig et al.	Brunner and Winter [1991]	
	Patient 1	Patient 2	Patient 3	Patient 4	Family 1	Family 2	[1990]	Family 1	Family 2
Microcephaly	+	+	+	+	+	+	+	+/–	+
Facial anomalies									
Short palpebral fissures	–	–	–	–	+	+	–	+	+
Micrognathia	–	–	–	–	+	?	+	–	–
Hand abnormalities									
Brachydactyly	2, 5	5	4,5	5	2, 5	2, 5	2, 5	2, 5	–
Clinodactyly	2, 4, 5	5	4,5	2, 4, 5	–	–	–	5	5
Foot abnormalities									
Syndactyly of toes	2–3, 4–5	2–3, 4–5	4–5	2–3, 4–5	2–3,	2–3,	2–3, 4–5	2–3, 4–5	–
Intestinal atresia/fistula									
Esophageal atresia/TOF[a]	–	–	–	–	+	–	+	+	–
Duodenal atresia	–	–	–	–	+	–	–	+	+
Development/ intelligence	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Learning disability	Normal

[a]Tracheoesophageal fistula.

TABLE II. Differential Diagnosis for Microcephaly With Digital Abnormalities

	Our patients				Feingold syndrome	Kelly syndrome	Filippi syndrome
	Patient 1	Patient 2	Patient 3	Patient 4			
Microcephaly	+	+	+	+	+	+	+
Growth retardation	–	–	–	–	–	+	+
Facial anomalies							
Epicanthus	–	–	–	+	–	–	–
Short palpebral fissures	–	–	–	–	+	–	–
Prominent nasal root	–	–	–	–	–	+	+
Hypoplastic alae nasi	–	–	–	–	–	–	+
Micrognathia	–	–	–	–	+	+	–
Hand abnormalities							
Brachydactyly	2, 5	5	4,5	5	2, 5	5	–
Clinodactyly	2, 4, 5	5	4,5	2, 4, 5	5	–	5
Syndactyly	–	–	–	–	–	–	2–3, 3–4
Foot abnormalities							
Long great toes	–	–	–	–	–	+	–
Syndactyly	4–5, 2–3	4–5, 2–3	4–5	4–5, 2–3	2–3, 4–5	2–4, 4–5	2–4, 4–5
Intestinal atresia/fistula							
Esophageal atresia/TOF[a]	–	–	–	–	+	–	–
Duodenal atresia	–	–	–	–	+	–	–
Development/intelligence	Normal	Normal	Normal	Normal	Normal	Severe MR	Severe MR
Inheritance		AD			AD	AR or XLR	AR

[a]Tracheoesophageal fistula.

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